220. A method as in claim 60, wherein the colloid particle has a self-assembled mixed monolayer of a plurality of molecules thereon.

221. A method as in claim 60, wherein the self-assembled monolayer is formed completely of synthetic molecules.

222. A method as in claim 60, wherein the self-assembled monolayer completely covers the colloid particle surface.

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223. A method as in claim 221, wherein the self-assembled monolayer completely covers the colloid particle surface.

224. A method as in claim 60, wherein at least one molecule forming the self-assembled monolayer comprises a thiol species terminating in a binding partner of an affinity tag.

225. A method as in claim 60, wherein the self-assembled monolayer on the colloid particle enables the colloid particle to resist non-specific adsorption without the need for treatment with a blocking protein.

226. A method as in claim 60, further comprising providing a plurality of colloid particles, each of which has a self-assembled monolayer of a plurality of molecules thereon, wherein the self-assembled monolayer is configured such that the particles can be maintained free of aggregation in a solution that is free of any detergents.

Remarks

This is in response to the Office Action mailed August 28, 2002.

In the Office Action, claims 39-59 and 85-181 were withdrawn from consideration. The remaining claims were rejected. However, the Office Action

indicated that claims 60-70, 72, 76, and 78-84 recite subject matter that is allowable over the prior art of record.

Regarding the amendments to the specification, the change to the paragraph on page 16 beginning at line 25 comprises the insertion of the chemical names corresponding to the acronym "EDC/NHS," where this acronym first appears in the specification. This insertion was suggested by the Examiners during the below-discussed telephone interview. The meaning of the above-mentioned abbreviation was well known to those skilled in the art of organic chemistry at the time of Applicants' invention, thus the insertion of the chemical names corresponding to the acronym does not constitute new matter.

The changes made to the paragraph on page 28 beginning at line 6 comprise a correction of a typographical error and a substitution of the word "molecule" for "wire" for clarity and consistency with the description in the remainder of the paragraph.

The new paragraph inserted on page 38, line 18 simply duplicates in the specification subject matter disclosed in Applicants' application by originally filed claims 63-65. As such, the insertion of this subject matter, previously disclosed in Applicants' originally-filed claims 63-65, does not constitute new matter.

Regarding the amendments to the claims, claims 60, 72, 76, and 78, each of which were identified in the Office Action as reciting subject matter allowable over the prior art of record, have each been rewritten in independent form to incorporate limitations of the claims from which they previously depended. Additionally, changes to claim 60 find support throughout Applicants' specification, for example, on page 21. The amendments to claims 3, 6, 13-15, 18-22, 26, 27, 29, 30, 32-38, 185, 189, and 190 involve changing the dependency of these rejected dependent claims so that they are now dependent, either directly or indirectly, upon claim 60, which has been rewritten in independent form. In certain cases, some of the amendments to these claims also involve minor changes in wording necessary for the claims to have proper antecedent basis for all their recited limitations in view of the change in their dependency. Claims 32 and 192 have been amended along similar lines as discussed immediately above, and, in addition, subject

matter related to the amendments of these claims can be found in Applicants' specification in, for example, Fig. 9 and on, for example, pages 11, 21, 26, and 36. Claim 189 has been amended along similar lines as discussed immediately above, and, in addition, subject matter related to the amendments of this claim can be found in Applicants' specification on, for example, pages 7, 23, 24, 27, 29, 33, 49, and 50.

After the above-mentioned claim amendments, cancellations, and addition of new claims, claims 3-8, 13-15, 18-70, 72, 76, 78-181, 185-190, 192, and 205-226 are pending, with claims 39-59 and 85-181 being withdrawn from consideration.

Telephone Interview with the Examiner and his Supervising Examiner

The Applicants thank Examiner Gary W. Counts and his supervisor, Examiner Long Le, for the courtesy of a telephone interview conducted on January 30, 2003, with Timothy J. Oyer and Michael J. Pomianek, Applicants' representatives, and inventor Dr. Cynthia C. Bamdad. The substance of the interview is summarized below.

During the interview, without conceding any of the merits of any of the prior art-based rejections made in the Office Action, Applicants' representatives stated Applicants' intention to obviate the prior art-based rejections by rewriting certain claims indicated as reciting allowable subject matter in the Office Action in independent form and either canceling, without prejudice, claims rejected over the prior art or rewriting such claims to depend from the rewritten claims. Accordingly, the remainder of the interview was directed to a discussion of the various rejections of the claims under 35 U.S.C. §112, ¶2 made in the Office Action. Each of the bases for rejection of the claims as lacking clarity under 35 U.S.C. §112, ¶2 as set forth in numbered paragraph 2 of the Office Action, was discussed. The Examiners made many helpful suggestions and, in certain cases, changes in language were proposed by Applicants' representatives that were sufficient to overcome certain of the objections. In other cases, the meaning and support for particular language was pointed out to the Examiners by Applicants' representatives and/or Dr. Bamdad and, it was agreed, that, in view of Applicants' specification, the objected to language was, in fact, sufficiently clear. The substance of

the specific discussions related to the individual objections raised in the Office Action to the claims under 35 U.S.C. §112, ¶2, and the agreement that was reached regarding the objections is discussed below in the section immediately below.

Response to the Rejections of Claims 1-38, 60-84, and 182-204 under 35 U.S.C. §112, ¶2

Reconsideration is respectfully requested of the rejection of the above-mentioned claims under 35 U.S.C. §112 ¶2 in view of the above amendments and remarks below.

a. In the Office Action, the preamble of claim 1 was objected to for lacking language indicating what the method is directed to. During the above-mentioned interview (hereinafter "the interview"), Applicants' representatives disagreed that such recitation was necessary to render the meaning and scope of the claim clear to those of ordinary skill in the art. Applicants' representatives noted that the claimed methods can be used for a wide variety of purposes and to achieve a wide variety of useful results, thereby rendering the recitation of any specific purpose or result in the preamble unduly limiting. Furthermore, Applicants' representatives stated that the purpose and scope of the claim would be clear to those skilled in the art upon reading the recited steps of the method, without the need for further clarification from the preamble. Nevertheless, solely for the purpose of expediting prosecution and allowance, Applicants have chosen to amend independent claims 60, 72, 76, and 78 to include in the preamble a recitation that the methods are directed to determining immobilization of a colloid particle relative to a non-colloidal structure. It is believed that this recitation is responsive to the concerns outlined in the Office Action and raised by the Examiners during the telephone interview. Moreover, because each of the above-mentioned claims recites in its body of a step of determining immobilization of the colloid particle relative to the non-colloidal structure, the addition of such recitation to the preamble, while perhaps enhancing readability, does not add any additional limitations to these claims.

b. In the Office Action, the language in claim 1, line 2 reciting "...allowing... the ability to become immobilized..." was objected to as being unclear. During the

interview, Applicants' representative proposed alternative language to clarify the intended meaning of the objected to language. The agreed-to language has been incorporated into rewritten independent claims 60, 72, 76, and 78 by the above amendments.

c. The recitation "allowing" in claim 6 and in other claims was objected to in the Office Action as being vague and unclear. This language has been amended in claims 6, 13, 14, and 21, in a manner similar to the amendments to claims 60, 72, 76, and 78 discussed in the paragraph immediately above, to overcome this basis of rejection.

d. The Office Action states that the recitation in claims 6 and 22 of a "plurality of colloid particles" is vague and indefinite in that it is not clear whether colloid particles are different from each other or the same. During the interview, Applicants' representatives explained that, as disclosed in Applicants' specification, depending on the particular application to which the claimed methods are directed, the plurality of colloid particles may, in fact, be different from each other or, in other instances, they may be substantially similar to each other. Thus, the meaning of this language as used in the context of these claims was, in fact, clearly understood by the Examiner as reflected in the Office Action; namely, the Examiner correctly understood that "plurality of colloid particles" can cover both a situation where the plurality of colloid particles include colloid particles that are different from each other as well as a situation where colloid particles are essentially the same. This correct, intended meaning of the above language would, similarly, be clearly understood by those skilled in the art.

e. In claim 9, which has now been incorporated into claims 60, 72, 76, and 78, the recitation "adapted," in the context of a biological or chemical agent being adapted for linkage to the non-colloidal structure, was objected to in the Office Action as being unclear. Other claims including similar recitations were objected to on the same basis. It was pointed out by Applicants' representatives in the interview that the meaning of the

term "adapted," used in the above and similar contexts, is clearly explained in Applicants' specification on page 16, lines 8-24 and on page 17, lines 11-14. In view of the detailed explanation provided in Applicants' specification for this terminology, it was agreed during the interview that this language was sufficiently clear. In addition, with regard to claim 9, the Office Action also objected to the use of the word "via" as being vague and indefinite. It was agreed during the interview that this language was sufficiently clear and that this basis for rejection would be withdrawn.

f. The recitation "the target" in claim 21 was objected to in the Office Action as lacking sufficient antecedent basis. It is believed that the present amendments to claim 21 overcome this basis for rejection.

g. The phrase "suspected of having the ability to bind to each other" in claim 22 and other claims was objected to as being vague and indefinite on the basis that it was unclear whether the agent and the binding partners actually become bound to each other. During the interview, Applicants' representatives explained that, as disclosed in Applicants' specification, in many embodiments of performing Applicants' claimed methods, the methods are utilized for the very purpose of determining whether or not a binding interaction will occur between the agents and suspected binding partners being tested. Such applications are disclosed and explained in Applicants' specification on, for example, page 24, line 23-page 27, line 2. Accordingly, it is believed that this language is clear and definite, especially in view of the present remarks and the above-referenced disclosure in Applicants' specification, and that the rejection on this basis has been overcome. Regarding the objection to the recitation of a "plurality of binding partners" in claim 22 raised in the Office Action, it is believed that this language is clear and definite for essentially the same reasons stated above with regard to the objection to the "plurality of colloid particles" recitation in the context of claim 6.

h. In the Office Action the terms "versus,", "vs.," and "exposing" were objected to as being unclear. During the interview, the Examiners agreed to withdraw their objection to "versus" and "exposing". It was agreed that when these terms as used in the context of the claims as read in view of Applicants' specification, they are sufficiently clear. Applicants' representatives did agree to replace the term "vs." with "versus" for consistency and clarity. This amendment has been made to claims 35-38.

i. The phrase "chelate coordinating a metal" in claim 31 was objected to in the Office Action as being vague. Applicants' representatives during the interview pointed out that this phrase is specifically defined in Applicants' specification on page 15, lines 12-14. It was agreed that in view of this specific definition that this phrase was sufficiently clear and understandable.

j. The phrase "having the ability" in the context of an enzyme having the ability to cleave the agent or binding partner recited in claim 63 was objected to in the Office Action as being vague and indefinite. The Office Action stated that it was unclear whether or not the enzyme actually cleaves the agent or binding partner. It was explained by Applicants' representatives during the interview that this phrase means that the enzyme has the intrinsic ability to cleave the agent or binding partner under certain predetermined conditions but may or may not actually cleave the agent or binding partner under the conditions of a particular test being conducted according to the method. Specifically, as disclosed in Applicants' specification on for example pages 37 and 38, methods as recited in claim 63 may be used for screening agents and/or conditions for the ability to inhibit the activity of the enzyme, such that it will not cleave the agent or binding partners under the particular conditions tested. Accordingly, it is believed that the meaning of the objected to language is clear and understandable, especially in view of these remarks and further in view of the above-referenced disclosure and other disclosure in Applicants' specification, and that the rejection on this basis has been overcome.

k. The objections raised to certain language in claim 71 have been rendered moot by the cancellation, without prejudice, of claim 71 herein. However, regarding the objection to the use of the term "moderation" in the context of moderation of activity of an enzyme, since this term is used in a similar context in pending claims 65, 70, 72, 76, 82, and 84, the objection to this language is addressed below. The Office Action states that the use of the term "moderation" in this context renders it unclear whether the candidate drug increases, decreases, or inhibits completely the activity of the enzyme. Applicants believe that it would be clear to those of skill in the art from the context of the claims in which the term appears and from Applicants' specification, especially on pages 36-38, that the terms "moderation" and "moderating" are intended to have their ordinary meaning, i.e., to reduce, abate, inhibit, etc.

l. The objections raised to certain language in claims 182 and 184 in the Office Action have been rendered moot by the cancellation, without prejudice, of these claims herein.

m. The term "defect sites" in claim 188 was objected to in the Office Action as being vague and indefinite. The Office Action states that it is unclear what Applicant intends by this term. As pointed out by Applicants' representatives during the interview, the meaning of this term is fully explained in Applicants' specification on page 19, lines 4-25. Specifically, as explained in the above-referenced disclosure, entities that cause defect sites in a self-assembled monolayer are entities that cause disruption of the tightly-packed self-assembled structure of the self-assembled monolayer, thereby allowing fluid to which the surface is exposed to communicate electrically with the surface. In view of the above remarks and the above-reference, disclosure and Applicants' specification, it is believed that the rejection of claim 188 on this basis has been overcome.

n. Regarding the objections raised with regard to lack of proper antecedent basis for certain limitations in claims 189 and 192 in the Office Action, it is believed that the

current amendments to claims 189 and 192 obviate these antecedent issues. The objection to the acronym "EDC/NHS" in claim 197 has been rendered moot by the cancellation, without prejudice, of this claim herein; however, as noted above, this acronym has been fully spelled out where it first appears in Applicants' specification via the amendment to the specification on page 16, line 25.

New Claims

New claims 205-226 have been added. Newly added independent claims 205 and 206 recite subject matter indicated as being allowable over the prior art of record on page 17 of the Office Action. The subject matter recited in new claim 205 can be found throughout Applicants' specification, for example on pages 18, 19, and 23. Similarly, subject matter recited in new claim 206 can be found throughout Applicants' specification, for example in Fig. 9 and on pages 25, 26, and 36.

New claim 207 depends from newly added independent claim 205 and recites subject matter disclosed in Applicants' specification on, for example, page 21.

New claims 208, 213, and 220 depend from new claim 207, new claim 206, and amended claim 60, respectively, and recite subject matter disclosed in Applicants' specification on, for example, page 20.

New claims 209, 214, and 221 depend from new claim 207, new claim 206, and amended claim 60, respectively, and recite subject matter disclosed in Applicants' specification on, for example, page 21.

New claims 210, 211, 215, 216, 222, and 223 depend from new claim 207, new claim 209, new claim 206, new claim 214, amended claim 60, and new claim 221, respectively, and recite subject matter disclosed in Applicants' specification on, for example, page 21.

New claims 212, 217, and 224 depend from new claim 207, new claim 206, and amended claim 60, respectively, and recite subject matter disclosed in Applicants' specification on, for example, pages 21 and 22.

New claims 218 and 225 depend from new claim 206 and amended claim 60, respectively, and recite subject matter disclosed in Applicants' specification on, for example, page 22.

New claims 219 and 226 depend from new claim 206 and amended claim 60, respectively, and recite subject matter disclosed in Applicants specification on, for example, page 22.

Conclusion

On the basis of the above remarks and amendments, it is believed that all of the objections to the claims as now pending have been removed or overcome, and a notice of allowance of the pending claims is respectfully requested. If, for any reason, the Examiner believes that a telephone conversation with Applicants' representative would expedite prosecution, the Examiner is requested to contact the undersigned at (617) 720-3500.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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Mailed: February 28, 2003
X02/28/03

Marked-Up Specification

Please rewrite the paragraph on page 16 at line 25 as follows:

"Covalently fastened" means fastened via nothing other than one or more covalent bonds. E.g. a species that is covalently coupled, via 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide (EDC/NHS) chemistry, to a carboxylate-presenting alkyl thiol which is in turn fastened to a gold surface, is covalently fastened to that surface.

Please rewrite the paragraph on page 28 at line 6, as follows:

"Molecular wires" as used herein, means [wires] molecules that enhance the ability for a fluid encountering a [SAM-coded] SAM-coated electrode to communicate electrically with the electrode. This includes conductive molecules or, as mentioned above and exemplified more fully below, molecules that can cause defects in the SAM allowing fluid contact with the electrode. A non-limiting list of additional molecular wires includes 2-mercaptopyridine, 2-mercaptobenzothiazole, dithiothreitol, 1, 2-benzenedithiol, 1, 2-benzenedimethanethiol, benzene-ethanethiol, and 2-mercaptoethylether. Conductivity of a monolayer can also be enhanced by the addition of molecules that promote conductivity in the plane of the electrode. Conducting SAMs can be composed of, but are not limited to: 1) poly (ethynylphenyl) chains terminated with a sulfur; 2) an alkyl thiol terminated with a benzene ring; 3) an alkyl thiol terminated with a DNA base; 4) any sulfur terminated species that packs poorly into a monolayer; 5) all of the above plus or minus alkyl thiol spacer molecules terminated with either ethylene glycol units or methyl groups to inhibit non specific adsorption. Thiols are described because of their affinity for gold in ready formation of a SAM. Other molecules can be substituted for thiols as known in the art from U.S. Patent No. 5,620,820, and other references.

Marked-Up Claims

3. **(Amended)** A method as in claim [1] 60, wherein the auxiliary signaling entity comprises a dye, pigment, electroactive molecule, chemiluminescent moiety, electrochemiluminescent moiety, fluorescent moiety, up-regulating phosphor, or enzyme-linked signaling moiety including horse radish peroxidase and alkaline phosphatase.

6. **(Amended)** A method as in claim [1] 60, comprising [allowing] providing a plurality of colloid particles [to fasten to] and the non-colloidal structure in proximity such that the plurality of colloid particles fasten to the non-colloidal structure, and determining fastening of the plurality of particles to the non-colloidal structure.

13. **(Amended)** A method as in claim [9] 60, comprising [allowing] providing the agent [to be] linked to the non-colloidal structure, the binding partner [to be] linked to the particle, and providing the colloid particle and the non-colloidal structure in proximity such that the agent and the binding partner [to] bind to each other.

14. **(Amended)** A method as in claim 13, comprising [allowing] providing the colloid particle and the non-colloidal structure in proximity such that the agent and the binding partner [to] biologically bind to each other.

15. **(Amended)** A method as in claim [9] 60, wherein the biological or chemical agent is a drug candidate, and the binding partner is a target of the drug candidate.

18. **(Amended)** A method as in claim [9] 60, wherein the biological or chemical agent is a nucleic acid sequence.

19. **(Amended)** A method as in claim [9] 60, wherein the biological or chemical agent is a peptide, and the binding partner is a binding partner of the peptide.

20. **(Amended)** A method as in claim [9] 60, wherein the biological or chemical agent is a protein, and the binding partner is a binding partner of the protein.

21. **(Amended)** A method as in claim [1] 60, wherein the colloid particle carries an immobilized ligand, and the non-colloidal structure carries a binding partner to the ligand, and wherein the step of providing [the method comprising allowing] the colloidal particle [the ability to fasten to] and the non-colloidal structure in proximity is performed in the presence of a candidate drug for interruption of binding of the ligand to the [target] binding partner.

22. **(Amended)** A method as in claim [1] 60, [wherein the non-colloidal structure is a bead,] further comprising providing a plurality of magnetic beads, a plurality of biological or chemical agents linked to or adapted for linkage to the beads, a plurality of colloid particles, and a plurality of binding partners of the biological or chemical agents linked to or adapted for linkage to the particles, wherein at least some of the agents and the binding partners are suspected of having the ability to bind to each other, the method comprising exposing at least some of the magnetic beads to at least some of the colloid particles, and determining immobilization of the colloid particles on the magnetic beads.

26. **(Amended)** A method as in claim [9] 60, comprising determining immobilization of the particle on the non-colloidal structure by determining a change in spectrum of absorbed or transmitted electromagnetic radiation interacting with the particle.

27. **(Amended)** A method as in claim [9] 60, comprising determining immobilization of the particles on the non-colloidal structure by visual inspection.

29. **(Amended)** A method as in claim [9] 60, wherein at least one of the agent or binding partner is linked to or adapted for linkage to the non-colloidal structure or particle, respectively, via an affinity tag/binding partner linkage.

30. **(Amended)** A method as in claim [9] 60, wherein at least one of the agent or binding partner is linked to or adapted for linkage to the non-colloidal structure or particle, respectively, via a metal binding tag/metal/chelate linkage.

32. **(Amended)** A method as in claim [9] 60, wherein [at least one of] the [agent or] binding partner is linked to or adapted for linkage to the [non-colloidal structure or] particle[, respectively,] via [a] the self-assembled monolayer and/or the agent is linked to or adapted for linkage to the magnetic bead via a self-assembled monolayer of a plurality of molecules thereon.

33. **(Amended)** A method as in claim [9] 60, wherein at least one of the agent or binding partner is linked to or adapted for linkage to the bead or particle, respectively, via complementary nucleic acid sequence pairs.

34. **(Amended)** A method as in claim [9] 60, wherein the binding partner is adapted for linkage to the particle via a glutathione/glutathione-s-transferase ligand interaction.

35. **(Amended)** A method as in claim [9] 60, comprising:

providing at least a first and a second [non-colloidal structure comprising polymeric] magnetic beads and at least a first and a second agent linked to the first and second beads, respectively;

providing a plurality of colloid particles each carrying immobilized thereto a suspected binding partner of the first and/or second agent;

exposing the beads to the particles; and

differentiating linkage of the particles to the first bead [vs.] versus the second bead.

36. **(Amended)** A method as in claim 35, wherein the first and second agents linked to the first and second [polymeric] magnetic beads are suspected of biological or chemical interaction with the binding partner, and the differentiating step comprises differentiating

biological interaction between the first agent and the binding partner [vs.] versus the second agent and the binding partner.

37. **(Amended)** A method as in claim [9] 60, comprising:

providing a plurality of [non-colloidal structures comprising] magnetic beads each carrying the agent immobilized thereto;

providing a first set and a second set of colloid particles, the first set each carrying immobilized thereto a first suspected binding partner of the agent and the second set each carrying immobilized thereto a second suspected binding partner of the agent;

exposing at least a first of the beads to the first set of particles and at least a second of the beads to the second set of particles;

differentiating linkage of the first set of particles to the first bead [vs.] versus the second set of particles to the bead.

38. **(Amended)** A method as in claim 37, wherein the first and second suspected binding partners are suspected of biological or chemical interaction with the agent, and the differentiating step comprises differentiating biological interaction between the agent and the first suspected binding partner [vs.] versus the agent and the second suspected binding partner.

60.**(Amended)** A method [as in claim 9,] for determining immobilization of a colloid particle relative to a non-colloidal structure comprising:

providing a biological or chemical agent linked to or adapted for linkage to a non-colloidal structure, and a binding partner of the biological or chemical agent linked to or adapted for linkage to a colloidal particle having a self-assembled monolayer of a plurality of molecules thereon;

providing the colloid particle and the non-colloidal structure in proximity such that, under at least one set of predetermined conditions, the colloid particle and the non-colloidal structure will become immobilized with respect to each other via the agent and the binding partner; and

determining immobilization of the colloid particle relative to the non-colloidal structure; wherein

the non-colloidal structure is a magnetic bead and the colloid particle comprises an auxiliary signaling entity.

72.**(Amended)** A method [as in claim 71,] for determining immobilization of a colloid particle relative to a non-colloidal structure comprising:

providing a colloid particle and a non-colloidal structure in proximity such that, under at least one set of predetermined conditions, the colloid particle and the non-colloidal structure will become immobilized with respect to each other;

exposing the colloid particle and the non-colloidal structure to an entity adapted for linkage both to the colloid particle and to the non-colloidal structure in the presence both of an enzyme having the ability to cleave the entity and a candidate drug for moderation of activity of the enzyme; and

determining immobilization of the colloid particle relative to the non-colloidal structure; wherein

the non-colloidal structure is a magnetic bead and the colloid particle carries an immobilized electroactive species, and wherein the [method comprising] determining step comprises

magnetically drawing the bead into proximity with an electrode, and determining proximity of the electroactive species to the electrode by activating the electrode thereby determining effectiveness of the drug candidate in inhibiting cleavage activity of the enzyme.

76.**(Amended)** A method [as in claim 74,] for determining immobilization of a colloid particle relative to a non-colloidal structure comprising:

providing a colloid particle and a non-colloidal structure in proximity such that, under at least one set of predetermined conditions, the colloid particle and the non-colloidal structure will become immobilized with respect to each other;

exposing the colloid particle and the non-colloidal structure to a substrate for an enzyme adapted for linkage to the non-colloidal structure, a molecular species linkable to the substrate via enzyme activity adapted for linkage to the particle, and an enzyme for the substrate; and

determining immobilization of the colloid particle relative to the non-colloidal structure; wherein

the non-colloidal structure is a magnetic bead and the colloid particle carries an immobilized electroactive entity, and wherein the [method comprising] determining step comprises

magnetically drawing the bead into proximity with an electrode, and determining proximity of the electroactive entity to the electrode by activating the electrode thereby determining effectiveness of the drug candidate in moderating activity of the enzyme.

78. A method [as in claim 74,] for determining immobilization of a colloid particle relative to a non-colloidal structure comprising:

providing a colloid particle and a non-colloidal structure in proximity such that, under at least one set of predetermined conditions, the colloid particle and the non-colloidal structure will become immobilized with respect to each other;

exposing the colloid particle and the non-colloidal structure to a substrate for an enzyme adapted for linkage to the non-colloidal structure, a molecular species linkable to the substrate via enzyme activity adapted for linkage to the particle, and an enzyme for the substrate; and

determining immobilization of the colloid particle relative to the non-colloidal structure; wherein

the non-colloidal structure is a magnetic bead.

185. **(Amended)** A method as in claim [183] 60, [further comprising a ligand and] wherein the signaling entity comprises an electroactive entity, and wherein the binding partner and the electroactive entity each [forming] form part of [a] the self-assembled monolayer [at a surface of] on the colloid particle.

189. **(Amended)** A method as in claim [104] 185, wherein the [[...]] comprises a ferrocene [dicarboxylic acid] derivitive.

190. **(Amended)** A method as in claim 185, wherein the [ligand] binding partner is linked to a self-assembled monolayer-forming species, which comprises at least one of the plurality of molecules forming the self-assembled monolayer, via a metal binding tag/metal/chelate linkage.

192. **(Amended)** A method as in claim [183] 60, wherein the [surface of the article] non-colloidal structure carries a self-assembled monolayer thereon.